

to a mammal in need of same, by spraying the oral mucosa of said mammal with a composition of claim 1.

18. (Amended) The composition of Claim 1 wherein the non-polar solvent is selected from the group consisting of (C<sub>2</sub>-C<sub>24</sub>) fatty acid (C<sub>2</sub>-C<sub>6</sub>) esters, C<sub>7</sub>-C<sub>18</sub> hydro-carbons of a linear or branched configuration, and C<sub>2</sub>-C<sub>6</sub> alkanoyl esters, and triglycerides of the corresponding acids.

19. (Amended) The composition of Claim 1 wherein the non-polar solvent is miglyol.

#### Remarks

The claims now in the application are claims 1-25, Claims 1, 12, 18 and 19 have been amended.

Applicants have carefully reviewed the outstanding Official Action, and, in part, traverse the rejection of certain claims under 35 U.S.C. § 112 second paragraph. With respect to Claim 1, applicant has amended the claim in the third and fifth paragraphs to differentiate between those compositions comprising a propellant and a polar solvent and those comprising a propellant and a non-polar solvent. In view of the Amendment, it is respectfully submitted that this claim now clearly recites the proper metes and bounds for all of the four various conditions for the spray. Namely, polar without propellant, polar with propellant, non-polar without propellant and non-polar with propellant.

It is respectfully submitted that no uncertainty is created by the further limitations in quantity set forth in the third and fifth paragraph which fall within but limit the quantities in the second and fourth paragraphs. It is further respectfully submitted that the Examiner is incorrect in designating a claim as vague and indefinite with respect to which

solvents are suitable for which active components. In the final paragraph, a selected but generic group of active compounds are set forth. Certain of these are soluble in polar solvents. Certain of them are soluble in non-polar solvents. Any pharmacologist would know which compounds belong in which group and therefore it is respectfully submitted that no uncertainty exists.

Applicant's undersigned attorney thanks the Examiner for pointing out the improper presence of a colon in the third paragraph which has been removed. The Examiner's comments with respect to Claims 6, 7, 18 and 19 as being vague and indefinite with respect to "the solvent" have been noted and, it is believed, that the designation of these solvents as respectively polar or non-polar resolves this issue. Furthermore, the typographical errors in Claims 8, 11, 12 and 18 have been noted and corrected. . In view of the foregoing comments and amendments, it is respectfully submitted that Claim 1 is now allowable under 35 U.S.C. § 112.

With respect to the rejections under 35 U.S.C. § 103, Applicant's undersigned attorney notes the discussions between the Examiner and Ms. Marcella Bodner, an associate of this office, with respect to the fact that the present application is a continuation in part of a PCT application having a filing date prior to that of the referenced Dugger patent 5,955,098. Hence, there was constructive reduction to practice of the present invention prior to the publication date of said Dugger reference and said Dugger reference is not available to the Examiner as grounds for rejection.

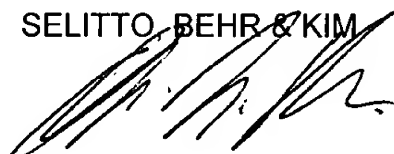
It should be noted that the PCT application in question is available to the Examiner in the files of the United States Patent and Trademark Office. However, in order to simplify the Examiner's task, Applicant's undersigned attorney has prepared a

comparison copy in which the material of the present application which was not present in the parent PCT application PHCO 3.0-005 is set forth as a somewhat gray underlined text and marked by vertical lines in the right margin and those items present in the said PCT document which are not present in the present application are indicated by strikeout.

It will be seen from this document that the present application is fully entitled to the priority of the parent PCT application, hence, the cited patent is not available to the Examiner as a primary reference and as a result thereof all claims as amended in the present application are allowable and a prompt passage to issue is respectfully solicited.

Respectfully submitted,

SELITTO, BEHR & KIM

A handwritten signature in black ink, appearing to be 'Omri M. Behr', written over the printed name.

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**Claim Text Showing Amendments**

**The claims now in the application are claims 1-25, Claims 1, 12, 18 and 19 have been amended as follows**

1. (Amended) A buccal spray composition for transmucosal administration of a pharmacologically active compound

provided that where the said active compound is soluble in a pharmacologically acceptable polar solvent said composition comprises in weight % of total composition: aqueous polar solvent 30-99.69%, active compound 0.001-60%,

where said composition in a polar solvent additionally comprises a propellant said composition comprises in total weight % of total composition: a propellant selected from the group consisting of C<sub>3-8</sub> hydrocarbon of a linear or branched configuration [ ]2 - 10%, aqueous polar solvent 10-99%, and active compound 0.1-25%,

where said active compound is soluble in a pharmacologically acceptable non-polar solvent said composition comprises in weight % of total composition: non-polar solvent 30-99.69%, active compound 0.005-55%, and

where said composition in a non-polar solvent additionally comprises a pharmaceutically acceptable propellant said composition comprises in weight % of total composition: a propellant selected from the group consisting of C<sub>3-8</sub> hydrocarbon of a linear or branched configuration 5-80%, non-polar solvent 20-85%, active compound 0.05-50%,

wherein the active compound is selected from the group consisting of bio-logically active peptides, central nervous system active amines, sulfonyl ureas, antibiotics, antifungals, antivirals, sleep inducers, antiasthmatics, antiemetics, histamine H-2 receptor antagonists, barbiturates, prostoglandins, bronchial dilators selected from the group consisting of terbutaline, and theophylline.

6. (Amended) The composition of Claim 1 wherein the polar solvent is aqueous polyethylene glycol.

7. (Amended) The composition of Claim 1 wherein the polar solvent comprises

aqueous ethanol.

8. (Amended) The composition of Claim 1 wherein the active compound is selected from the group consisting of cyclosporin, clozapine, zidevudine, erythromycin, [odansetron,] ondansetron, cimetidine, phenytoin, carboprost thromethamine, and valerian in their nonionized form or as the pharmaceutically acceptable salts thereof.

11. (Amended) The composition of Claim 2 of the formulation: polar solvent 19-90%, [odansitron] ondansetron hydrochloride 2.5-15%, flavoring agent 1-10%.

12. (Amended) A method of administering a pharmacologically active compound to a mammal in [needed] need of same, by spraying the oral mucosa of said mammal with a composition of claim 1.

18. (Amended) The composition of Claim 1 wherein the non-polar solvent is [a] selected from the group consisting of (C<sub>2</sub>-C<sub>24</sub>) fatty acid (C<sub>2</sub>-C<sub>6</sub>) esters, C<sub>7</sub>-C<sub>18</sub> hydro-carbons of a linear or branched configuration, and C<sub>2</sub>-C<sub>6</sub> alkanoyl esters, and triglycerides of the corresponding acids.

19. (Amended) The composition of Claim 1 wherein the non-polar solvent is miglyol.

#5

TITLE OF THE INVENTION

BUCCAL, POLAR AND NON-POLAR SPRAY OR CAPSULE

RELATED APPLICATIONS

- 5    This application is a continuation in part of applicant PCT application  
PCT/US97/17899 filed October 1<sup>st</sup> 1997.

BACKGROUND OF THE INVENTION

10    It is known that certain biologically active compounds are better  
absorbed through the oral mucosa than through other routes of administration,  
such as through the stomach or intestine. However, formulations suitable for  
such administration by these latter routes present their own problems. For  
example, the biologically active compound must be compatible with the other  
components of the composition such as propellants, solvents, etc. Many such  
15    formulations have been proposed. For example, U.S.P. 4,689,233, Dvorsky et  
al., describes a soft gelatin capsule for the administration of the anti-coronary  
drug nifedipine dissolved in a mixture of polyether alcohols. U.S.P. 4,755,389,  
Jones et al., describes a hard gelatin chewable capsule containing nifedipine.  
A chewable gelatin capsule containing a solution or dispersion of a drug is  
20    described in U.S.P. 4,935,243, Borkan et al. U.S.P. 4,919,919, Aouda et al.,  
and U.S.P. 5,370,862, Klokke-Bethke, describe a nitroglycerin spray for  
administration to the oral mucosa comprising nitroglycerin, ethanol, and other  
components. An orally administered pump spray is described by Cholcha in  
U.S.P. 5,186,925. Aerosol compositions containing a hydrocarbon propellant  
25    and a drug for administration to a mucosal surface are described in U.K.  
2,082,457, Su, U.S.P. 3,155,574, Silson et al., U.S.P. 5,011,678, Wang et al.,  
and by Parnell in U.S.P. 5,128,132. It should be noted that these references  
discuss bioavailability of solutions by inhalation rather than through the  
membranes to which they are administered.

30

SUMMARY OF THE INVENTION

A buccal aerosol spray or soft bite gelatin capsule using a polar ~~and/or~~ non-polar solvent has now been developed which provides biologically active compounds for rapid absorption through the oral mucosa, resulting in fast onset of effect.

5

The buccal aerosol spray compositions of the present invention, for transmucosal administration of a pharmacologically active compound soluble in a pharmacologically acceptable non-polar solvent ~~comprising~~comprise in weight % of total composition: pharmaceutically acceptable propellant 5-80%,  
10 non-polar solvent 20-84.85%, active compound 0.05-50%, suitably additionally comprising, by weight of total composition a flavoring agent 0.01-10%. Preferably the composition comprises: propellant 10-85%, non-polar solvent 25-89.9%, active compound 0.01-40%, flavoring agent 1-8%; most suitably propellant 20-70%, non-polar solvent 30-74.75%, active compound 0.25-35%,  
15 flavoring agent 2-7.5%.

The buccal polar aerosol spray compositions of the present invention, for transmucosal administration of a pharmacologically active compound soluble in a pharmacologically acceptable polar solvent are also administrable  
20 in aerosol form driven by a propellant. In this case the composition comprise in weight% of total composition: aqueous polar solvent 10-99%, active compound 0.1-25%, suitably additionally comprising, by weight of total composition a flavoring agent 0.05-10% and propellant: 2 - 10%. Preferably the composition  
comprises: polar solvent 20 - 97%, active compound 0.1-15%, flavoring agent  
25 0.1-5% and propellant: 3 - 5%; most suitably polar solvent 25 - 97%, active compound 0.2-25%, flavoring agent 0.1-2.5% and propellant: 3 - 4%.

The buccal pump spray composition of the present invention for  
30 transmucosal administration of a pharmacologically active compound where said active compound is soluble in a pharmacologically acceptable non-polar

solvent said composition comprise in weight % of total composition: non-polar solvent 30-99.69%, active compound 0.005-55%, and suitably additionally, flavoring agent 0.1-10%.

- 5           The buccal polar pump spray compositions of the present invention, for transmucosal administration of a pharmacologically active compound soluble in a pharmacologically acceptable polar solvent comprising in weight% of total composition: aqueous polar solvent 30-99.69%, active compound 0.001-60%, suitably additionally comprising, by weight of total composition a flavoring agent
- 10 0.1-10%. Preferably the composition comprises: polar solvent 37-98.58%, active compound 0.005-55%, flavoring agent 0.5-28%; most suitably polar solvent 60.9-97.06%, active compound 0.01-40%, flavoring agent 0.75-7.5%.

- 15           The soft bite gelatin capsules of the present invention for transmucosal administration of a pharmacologically active compound, at least partially soluble in a pharmacologically acceptable non-polar solvent, having charged thereto a fill composition ~~comprising in weight % of total composition: non-polar solvent~~ comprise in weight % of total composition: 34-99.99%, non-polar solvent 4-99.99%, emulsifier 0-20%, active compound 0.01-80%, provided that said fill
- 20 composition contains less than 10% of water, suitably additionally comprising, by weight of the composition: flavoring agent 0.01-10%. Preferably, the soft bite gelatin capsule comprises: non-polar solvent 21.5-99.975%, emulsifier 0-15%, active compound 0.025-70%, flavoring agent 1-8%; most suitably: non-polar solvent 28.5-97.9%, emulsifier 0-10%, active compound 0.1-65.0%,
- 25 flavoring agent 2-6%.

- The soft bite polar gelatin capsules of the present invention for transmucosal administration of a pharmacologically active compound, at least partially soluble in a pharmacologically acceptable polar solvent, having
- 30 charged thereto a composition comprising in weight % of total composition: polar solvent 25-99.89%, emulsifier 0-20%, active compound 0.01-65%,



provided that said composition contains less than 10% of water, suitably additionally comprising, by weight of the composition: flavoring agent 01-10%. Preferably, the soft bite gelatin capsule comprises: polar solvent 37-99.95%, emulsifier 0-15%, active compound 0.025-55%, flavoring agent 1-8%; most  
5 suitably: polar solvent 44-96.925%, emulsifier 0-10%, active compound 0.075-50%, flavoring agent 2-6%.

It is an object of the invention to coat the mucosal membranes either with extremely fine droplets of spray containing the active compounds or a  
10 solution or paste thereof from bite capsules.

It is also an object of the invention to administer to the oral mucosa of a mammalian in need of same, preferably man, by spray or bite capsule. a predetermined amount of a biologically active compound by this method or  
15 from a soft gelatin bite capsule.

A further object is a sealed aerosol spray container containing a composition of the non polar or polar aerosol spray formulation, and a metered valve suitable for releasing from said container a predetermined amount of said  
20 composition.

As the propellant evaporates after activation of the aerosol valve, a mist of fine droplets is formed which contains solvent and active compound.

The propellant is a non-Freon material, preferably a C<sub>3-8</sub> hydrocarbon of  
25 a linear or branched configuration. The propellant should be substantially non-aqueous. The propellant produces a pressure in the aerosol container such that under expected normal usage it will produce sufficient pressure to expel the solvent from the container when the valve is activated but not excessive pressure such as to damage the container or valve seals.

30

The ~~non-polar~~non-polar solvent is a non-polar hydrocarbon, preferably a

C<sub>7-18</sub> hydrocarbon of a linear or branched configuration, fatty acid esters, and triglycerides, such as miglyol. The solvent must dissolve the active compound and be miscible with the propellant, i.e., solvent and propellant must form a single phase at 0-40°C at a pressure range of 1-3 atm.

5

Then ~~non~~ polar and non-polar aerosol spray compositions of the invention are intended to be administered from a sealed, pressurized container. Unlike a pump spray, which allows the entry of air into the container after every activation, the aerosol container of the invention is sealed at the time of  
10 manufacture. The contents of the container are released by activation of a metered valve, will does not allow entry of atmospheric gasses with each activation. Such containers are commercially available.

A further object is a pump spray container containing a composition of  
15 the pump spray formulation, and a metered valve suitable for releasing from said container a predetermined amount of said composition.

A further object is a soft gelatin bite capsule containing a composition of as set forth above. The formulation may be in the form of a viscous solution or  
20 paste containing the active compounds. Although solutions are preferred, paste fills may also be used where the active compound is not soluble or only partially soluble in the solvent of choice. Where water is used to form part of the paste composition, it should not exceed 10% thereof. (All percentages herein are by weight unless otherwise indicated.)

25

The polar or non-polar solvent is chosen such that it is compatible with the gelatin shell and the active compound. The solvent preferably dissolves the active compound. However, other components wherein the active compound is not soluble or only slightly soluble may be used and will form a  
30 paste fill.

Soft gelatin capsules are well known in the art. See, for example, U.S.P. 4,935,243, Borkan et al., ~~which is incorporated herein by reference~~ for its teaching of such capsules. The capsules of the present invention are intended to be bitten into to release the low viscosity solution or paste therein, which will then coat the buccal mucosa with the active compounds. Typical capsules, which are swallowed whole or bitten and then swallowed, deliver the active compounds the stomach, which results in significant lag time before maximum blood levels can be achieved or subject the compound to a large first pass effect. Because of the enhanced absorption of the compounds through the oral mucosa and no chance of a first pass effect, use of the bite capsules of the invention will eliminate much of the lag time, resulting in hastened onset of biological effect. The shell of a soft gelatin capsule of the invention may comprise, for example:

gelatine 50-75%, ~~glycerine~~ Gelatin: 50-75%, glycerin 20-30%, colorants 0.5-1.5%, water 5-10%, and sorbitol 2-10%.

The active compound may include biologically active peptides, central nervous system active amines, sulfonyl ureas, antibiotics, antifungals, antivirals, sleep inducers, antiasthmatics, bronchial dilators, antiemetics, histamine H-2 receptor antagonists, barbiturates, prostaglandins and neutraceuticals.

The active compounds may also include antihistamines, alkaloids, hormones, benzodiazepines and narcotic analgesics. While not limited thereto, these active compounds are particularly suitable for non-polar pump spray formulation and application.

#### BRIEF DESCRIPTION OF THE DRAWING

The figure is a schematic diagram showing routes of absorption and processing of pharmacologically active substances in a mammalian system.

### DESCRIPTION OF THE PREFERRED EMBODIMENTS

The preferred active compounds of the present invention are in their ~~nonionized~~ an ionized, salt form or as the free base of the pharmaceutically acceptable salts thereof (provided, for the aerosol or spray compositions, they are soluble in the spray solvent), ~~as well as, where appropriate the esters or triglycerides thereof.~~ These compounds are soluble in the non-polar solvents of the invention at useful concentrations or can be prepared as pastes at useful concentrations. These concentrations may be less than the standard accepted dose for these compounds since there is enhanced absorption of the compounds through the oral mucosa. This aspect of the invention is especially important when there is a large (40-99.99%) First pass effect.

As propellants for the non polar sprays, propane, N-butane, ~~iso-butane,~~ iso-butane, N-pentane, iso-pentane, and neo-pentane, and mixtures thereof may be used. N-butane and iso-butane, as single gases, are the preferred propellants. It is permissible for the propellant to have a water content of no more than 0.2%, typically 0.1-0.2%. (All percentages herein are by weight unless otherwise indicated.) It is also preferable that the propellant be synthetically produced to minimize the presence of contaminants which are harmful to the active compounds. These contaminants include oxidizing agents, reducing agents, Lewis acids or bases, and water. The concentration of each of these should be less than 0.1%, except that water may be as high as 0.2%.

Suitable non-polar solvents for the capsules and the non-polar sprays include (C<sub>2</sub>-C<sub>24</sub>) fatty acid C<sub>2</sub>-C<sub>6</sub> esters, ~~the above listed C<sub>7</sub>-C<sub>18</sub> hydrocarbon~~ C<sub>7</sub>-C<sub>18</sub> hydrocarbon, C<sub>2</sub>-C<sub>6</sub> alkanoyl esters, and the triglycerides of the alcohols thereof. Similarly, ~~water is not a suitable solvent component in the spray compositions.~~ corresponding acids. When the capsule fill is a paste,

other liquid components may be used instead of the above low molecular weight solvents. These include soya oil, corn oil, other vegetable oils, and  $C_{7-18}$  hydrocarbons of a linear or branched configuration, and their alcohols and their fatty acid esters and triglycerides.

As solvents for the polar capsules or sprays there may be used low molecular weight polyethyleneglycols (PEG) of 400-1000 Mw (preferably 400-600), low molecular weight (C<sub>2</sub>-C<sub>8</sub>) mono and polyols, ~~such as glycerin may also be present and water may also be used.~~

5 polyols and alcohols of C<sub>7</sub>-C<sub>18</sub> linear or branch chain hydrocarbons, glycerin may also be present and

~~———— Suitable polar solvents for the capsules include low molecular weight polyethyleneglycols (PEG) of 400-1000 Mw (preferably 400-600). Low molecular weight alcohols and polyols, such as glycerin may also be present and water may also be used. However, these should only be used sparingly in the bite capsule compositions as they may migrate into the gelatin shell and weaken it. water may also be used in the sprays, but only in limited amount in the capsules.~~

10

15 It is expected that some glycerin and water used to make the gelatin shell will migrate from the shell to the fill during the curing of the shell. Likewise, there may be some migration of components from the fill to the shell during curing and even throughout the shelf-life of the capsule. Therefore, the values given herein are for the compositions as prepared, it being within the scope of the invention that minor variations will occur.

20

The preferred flavoring agents are synthetic or natural oil of peppermint, oil of spearmint, citrus oil, fruit flavors, sweeteners (sugars, aspartame, saccharin, etc.), and combinations thereof.

25

The active substances include the active compounds selected from the group consisting of

cyclosporine, sermorelin, Octreotide acetate, cal-citonin-salmon, insulin lispro, sumatriptan succinate, clozapine, cyclo-benzaprine, dexfenfluramine

30 hydrochloride, glyburide, zidovudine, erythro-mycin,

~~———— ciprofloxacin, ondansetron hydrochloride, dimenhydrinate, cimetidine~~

hydrochloride, famotidine, phenytoin sodium, phenytoin, carboprost thro-  
methamine, carboprost, diphenhydramine hydrochloride, isoproterenol  
hydrochloride, terbutaline sulfate, terbutaline, theophylline, albuterol sulfate and  
neutraceuticals, that is to say nutrients with pharmacological action such as but  
5 not limited to carnitine, valerian, echinacea, and the like.

The formulations of the present invention comprise an active com-  
pound or a pharmaceutically acceptable salt thereof. The term  
"pharmaceutically acceptable salts" refers to salts prepared from  
10 pharmaceutically acceptable non-toxic acids or bases including organic and  
inorganic acids or bases.

When an active compound of the present invention is acidic, salts may  
be prepared from pharmaceutically acceptable non-toxic bases. Salts derived  
15 from all stable forms of inorganic bases include aluminum, ammonium,  
calcium, copper, iron, lithium, magnesium, manganese, potassium, sodium,  
zinc, etc. Particularly preferred are the ammonium, calcium, magnesium,  
potassium, and sodium salts. Salts derived from pharmaceutically acceptable  
organic non-toxic bases include salts of primary, secondary, and tertiary  
20 amines, substituted amines including naturally occurring substituted amines,  
cyclic amines and basic ion- exchange resins such as arginine, betaine,  
caffeine, choline, N,N'- dibenzylethylenediamine, diethylamine,  
2-diethylaminoethanol, 2-dimethyl-aminoethanol, ethanolamine,  
ethylenediamine, N-ethylmorpholine, N-ethyl-piperidine, glucamine,  
25 glucosamine, histidine, isopropylamine, lysine, methyl-glucosamine,  
morpholine, piperazine, piperidine, polyamine resins, procaine, purine,  
theobromine, triethylamine, trimethylamine, tripropylamine, etc.

When an active compound of the present invention is basic, salts may  
30 be prepared from pharmaceutically acceptable non-toxic acids. Such acids  
include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethane-

sulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, mandelic, methanesulfonic, mucic, nitric, pamoic, panto-thenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic, etc. Particularly preferred are citric, hydrobromic, maleic, phosphoric, sulfuric, and tartaric acids.

In the discussion of methods of treatment herein, reference to the active compounds is meant to also include the pharmaceutically acceptable salts thereof. While certain formulations are set forth herein, the actual amounts to be administered to the mammal or man in need of same are to be determined by the treating physician.



The invention is further defined by reference to the following examples, which are intended to be illustrative and not limiting.

\_\_\_\_\_The following are examples of each class ( all values unless otherwise specified are in weight percent):

### EXAMPLE 1

#### 5 **Biologically active peptides including peptide hormones**

##### A. Cyclosporine lingual spray

	Amounts	preferred amount	most preferred amount
Cyclosporine	5-50	10-35	15-25
water	5-20	7.5-50	9.5-12
10 ethanol	5-60	7.5-50	10-20
polyethylene glycol	20-60	30-45	35-40
flavors	0.1-5	1-4	2-3

##### B. Cyclosporine Non-Polar lingual spray

	Amounts	preferred amount	most preferred amount
Cyclosporine	1-50	3-40	5-30
Migylol	25-50	35-45	30-40
<u>Migylol</u>	<u>20</u>	<u>25</u>	<u>30-40</u>
<del>Polyoxyethyl-ated</del>	<del>25-50</del>	<del>35-45</del>	<del>30-40</del>
castor oil			
<u>Polyoxyethyl-ated</u>	<u>20</u>	<u>25</u>	<u>30-40</u>
<u>castor oil</u>			
Butane	25-80	30-70	33-50
flavors	0.1-5	1-4	2-3

**C. Cyclosporine non-polar bite capsule**

	Amounts	preferred amount	most preferred amount
Cyclosporine	1-35	5-25	10-20
olive oil	25-60	35-55	30-45
polyoxyethyl-ated	25-60	35-55	30-45
oleic glycerides			
flavors	0.1-5	1-4	2-3

**C.D. Cyclosporine bite capsule**

	Amounts	preferred amount	most preferred amount
Cyclosporine	5-50	10-35	15-25
5 polyethylene glycol	20-60	30-45	35-40
glycerin	5-30	7.5-25	10-20
propylene glycol 5-30	7.5-25	10-20	
flavors	0.1-10	1-8	3-6

**10 E. Sermorelin (as the acetate) lingual spray**

	Amounts	preferred amount	
most amount	most preferred	sermorelin (as the acetate)	.01-5 .1-3
	.2-1.0		
mannitol,	1-25	5-20	10-15
15 monobasic sodium phosphate,	0.1-5	1-3	1.5-2.5
dibasic sodium phosphate water	0.01-5	.05-3	0.1-0.5
ethanol	5-30	7.5-25	9.5-15
polyethylene glycol	20-60	30-45	35-40
propylene glycol	5-25	10-20	12-17
20 flavors	0.1-5	1-4	2-3

F. Octreotide acetate (Sandostatin®) lingual spray

	Amounts	preferred amount	most preferred amount
octreotide acetate	0.001-0.5	0.005-0.250	0.01-0.10
acetic acid	1-10	2-8	4-6
5 sodium acetate	1-10	2-8	4-6
sodium chloride	1-10	2-8	4-6
<u>sodium chloride</u>	3-30	5-25	15-20
flavors	0.1-5	0.5-4	2-3
ethanol	5-30	7.5-20	9.5-15
10 water	15-95	35-90	65-85
flavors	0.1-5	1-4	2-3

**G. Calcitonin-salmon lingual spray**

	Amounts	preferred amount	most preferred amount
Calcitonin-salmon	0.001-5 0.005-2	0.01-1.5	
5 ethanol	0.005-2 0.1-1.5		
ethanol	2-15	3-10	7-9.5
water	30-95	50-90	60-80
polyethylene glycol	2-15	3-10	7-9.5
sodium chloride	2.5-20 5-15	10-12.5	
10 flavors	0.1-5 1-4	2-3	

**H. insulin lispro, lingual spray**

	Amounts	preferred amount	most preferred amount
insulin, (units/activation)	25-1000	50-800	100-500
15	20-60 4-55	5-50	
glycerin,	0.1-10	0.25-5	0.1-1.5
dibasic sodium phosphate,	1-15	2.5-10	4-8
m-cresol,	1-25	5-25	7.5-12.5
zinc oxide	0.01-0.25	.05-0.15	0.075-0.10
20 m-cresol,	0.1-1	0.2-0.8	0.4-0.6
phenol	trace amounts	trace amounts	trace amounts
ethanol	5-20	7.5-15	9-12
water	30-90	40-80	50-75
propylene glycol	5-20	7.5-15	9-12
25 flavors	0.1-5	0.5-3	0.75-2
adjust pH to 7.0-7.8 with HCl or NaOH			

## EXAMPLE 2

CNS active amines and their salts: including but not limited to tricyclic amines, GABA analogues, thiazides, phenothiazine derivatives, Serotonin Serotonin antagonists and serotonin antagonists and serotonin

## 5 reuptake inhibitors

A. Sumatriptan succinate lingual spray

	Amounts	preferred amount	most preferred amount
sumatriptan succinate	0.5-30	1-20	10-15
ethanol	5-60	7.5-50	10-20
10 propylene glycol	5-30	7.5-20	10-15
polyethylene glycol	0-60	30-45	35-40
water	5-30	7.5-20	10-15
flavors	0.1-5	1-4	2-3

15 B. Sumatriptan succinate bite capsule

	Amounts	preferred amount	most preferred amount
sumatriptan succinate	0.01-5	0.05-3.5	0.075-1.75
polyethylene glycol	20-60	30-45	35-40
glycerin	5-30	7.5-25	10-20
20 60	35-50		25-70
glycerin	25-70	30-60	35-50
flavors	0.1-10	1-8	3-6

C. Clozapine lingual spray

	Amounts	preferred amount	most preferred amount
25 Clozapine	0.5-30	1-20	10-15
ethanol	0.5-30	1-20	10-15
ethanol	5-60	7.5-50	10-20
propylene glycol	5-30	7.5-20	10-15
30 polyethylene glycol	0-60	30-45	35-40
water	5-30	7.5-20	10-15
flavors	0.1-5	1-4	2-3

**D. ClozapineClozepine Non-Polar lingual spray with propellant**

	Amounts	preferred amount	most preferred amount
Clozapine	0.5-30	1-20	10-15
<u>Clozepine</u>	<u>0.5-30</u>	<u>1-20</u>	<u>10-15</u>
Migylol	20-85	25-70	30-40
Butane	15-80	30-75	60-70
flavors	0.1-5	1-4	2-3

**E. ClozapineClozepine Non-Polar lingual spray without propellant**

	Amounts	preferred amount	most preferred amount
Clozapine	0.5-30	1-20	10-15
<u>Clozepine</u>	<u>0.5-30</u>	<u>1-20</u>	<u>10-15</u>
Migylol	70-99.5	80-99	85-90
flavors	0.1-5	1-4	2-3



**F. Cyclobenzaprine Non polar lingual spray**

	Amounts	preferred amount	most preferred amount
Cyclobenzaprine (base)	0.5-30	1-20	10-15
Migylol	20-85	25-70	30-40
Iso-butane flavors	15-80	30-75	60-70
	0.1-5	1-4	2-3

**G. dexfenfluramine hydrochloride lingual spray**

5		Amounts	preferred amount	most	preferred
	amount	<u>most preferred</u>			
	dexfenfluramine HCl	5-30	7.5-20	10-15	
	ethanol	5-60	7.5-50	10-20	
	propylene glycol	5-30	7.5-20	10-15	
10	polyethylene glycol	0-60	30-45	35-40	
	water	5-30	7.5-20	10-15	
	flavors	0.1-5	1-4	2-3	

			amount	amount
15	dexfenfluramine Hcl	5-30	7.5-20	10-15
	ethanol	5-60	7.5-50	10-20
	propylene glycol	5-30	7.5-20	10-15
	polyethylene glycol	0-60	30-45	35-40
	water	5-30	7.5-20	10-15
20	flavors	0.1-5	1-4	2-3

## EXAMPLE 3

**Sulfonylur as****A. Glyburide lingual spray**

5		Amounts	preferred amount	most preferred amount
	Glyburide	0.25-25	0.5-20	0.75-15
	ethanol	5-60	7.5-50	10-20
	propylene glycol 5-30	7.5-20	10-15	
	polyethylene glycol	0-60	30-45	35-40
10	water	2.5-30	5-20	6-15
	flavors	0.1-5	1-4	2-3

**B. Glyburide non-polar bite capsule**

	Amounts	preferred amount	most preferred amount
Glyburide	0.01-10	0.025-7.5	0.1-4
olive oil	25-50	35-45	30-40
<u>olive oil</u>	<u>30-60</u>	<u>35-55</u>	<u>30-50</u>
polyoxyethyl-ated	25-50	35-45	30-40
oleic glycerides			
<u>polyoxyethyl-ated</u>	<u>30-60</u>	<u>35-55</u>	<u>30-50</u>
<u>oleic glycerides</u>			
flavors	0.1-5	1-4	2-3
<u>flavors</u>	<u>0.1-5</u>	<u>1-4</u>	<u>2-3</u>

**EXAMPLE 4****Antibiotics anti-fungals and anti-virals**

5

**A. zidovudine [formerly called azidothymidine (AZT) (Retrovir) non-polar  
lingual  
lingual \_\_\_\_\_ spray**

	Amounts	preferred amount	most preferred amount
zidovudine	10-50	15-40	25-35
Soya oil	20-85	25-70	30-40
Butane	15-80	30-75	60-70
flavors	0.1-5	1-4	2-3

**B. Erythromycin bite capsule bite capsule**

	Amounts	preferred amount	most preferred amount
Erythromycin	25-65		
triglyceride	50-75		
5 glycerin	10-15		
flavors	1-10 25-65	30-50	35-45
polyoxyethylene glycol	5-70	30-60	45-55
glycerin	5-20	7.5-15	10-12.5
flavors	1-10	2-8	3-6

10

**C. Ciprofloxacin hydrochloride bite capsule**

	Amounts	preferred amount	most preferred amount
Ciprofloxacin hydrochloride	25-65	35-55	40-50
glycerin	5-20	7.5-15	10-12.5
15 polyethylene glycol	20-75	30-65	40-60
flavors	1-10	2-8	3-6

**D. zidovudine [formerly called azidothymidine (AZT) (Retrovir) lingual spray**

		Amounts	preferred amount	most preferred amount
5	zidovudine	10-50	15-40	25-35
	water	30-80	40-75	45-70
	ethanol	5-20	7.5-15	9.5-12.5
	polyethylene glycol	5-20	7.5-15	9.5-12.5
	flavors	0.1-5	1-4	2-3

10

**EXAMPLE 5****Anti-emetics****A. Ondansetron hydrochloride lingual spray**

		Amounts	preferred amount	most preferred amount
15	ondansetron hydrochloride	1-25	2-20	2.5-15
	citric acid monohydrate, _____	1-10	2-8	2.5-5
	sodium citrate dihydrate 0.5-5	1-4		1.25-2.5
	water	1-90	5-85	10-75
	ethanol	5-30	7.5-20	9.5-15
20	propylene glycol	5-30	7.5-20	9.5-15
	polyethylene glycol	5-30	7.5-20	9.5-15
	flavors	1-10	3-8	5-7.5

**B. Dimenhydrinate bite capsule**

		Amounts	preferred amount	most preferred amount
Dimenhydrinate		0.5-30	2-25	3-15
glycerin		5-20	7.5-15	10-12.5
5	polyethylene glycol	20-75	30-65	40-60
		7.5-15	10-12.5	5-20
polyethylene glycol		45-95	50-90	55-85
flavors		1-10	2-8	3-6

**C. Dimenhydrinate polar lingual spray**

	Amounts	preferred amount	most preferred amount
Dimenhydrinate	3-50	4-40	5-35
water	5-90	10-80	50-75
<u>water</u>	<u>5-90</u>	<u>10-80</u>	<u>15-75</u>
ethanol	1-80	3-50	5-10
polyethylene glycol	1-80	3-50	5-15
Sorbitol	0.1-5	0.2-4	0.4-1.0
aspartame	0.01-0.5	0.02-0.4	0.04-0.1
flavors	0.1-5	1-4	2-3

**EXAMPLE 6**

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**Histamine H-2 receptor antagonists****A. Cimetidine hydrochloride bite capsule**

	Amounts	preferred amount	most preferred amount
Cimetidine HCl	10-60	15-55	25-50
10 glycerinHcl	10-60	15-55	25-50
<u>glycerin</u>	5-20	7.5-15	10-12.5
polyethylene glycol	20-90	25-85	30-75
flavors	1-10	2-8	3-6

15

**B. Famotidine lingual spray**

	Amounts	preferred amount	most preferred amount
Famotidine	1-35	5-30	7-20
water	2.5-25	3-20	5-10
L-aspartic acid	0.1-20	1-15	5-10
20 polyethylene glycol	20-97	30-95	50-85
flavors	0.1-10	1-7.5	2-5

C. Famotidine non-polar lingual spray

	Amounts	preferred amount	most preferred amount
zidovudine	1-35	5-30	7-20
<u>Famotidine</u>	<u>1-35</u>	<u>5-30</u>	<u>7-20</u>
Soya oil	10-50	15-40	15-20
Butane	15-80	30-75	60-70
<u>Butane</u>	<u>15-80</u>	<u>30-75</u>	<u>45-70</u>
polyoxyethyl-ated oleic glycerides	10-50	15-40	15-20
flavors	0.1-5	1-4	2-3

## EXAMPLE 7

## Barbiturates

5

A. Phenytoin sodium lingual spray

	Amounts	preferred amount	most preferred amount
Phenytoin sodium	10-60	15-55	20-40
water	10-60	15-55	20-40
<u>water</u>	2.5-25	3-20	5-10
ethanol	5-30	7.5-20	9.5-15
propylene glycol	5-30	7.5-20	9.5-15
polyethylene glycol	5-30	7.5-20	9.5-15
flavors	1-10	3-8	5-7.5

15

B. Phenytoin non-polar lingual spray

	Amounts	preferred amount	most preferred amount
Phenytoin	5-45	10-40	15-35
migylol	10-50	15-40	15-20
Butane	15-80	30-75	60-70
polyoxyethyl-ated oleic glycerides	10-50	15-40	15-20
flavors	0.1-10	1-8	5-7.5



970917 RV3 000322 RV1

32

PHCO3.0-008CIPHC03.0-00530

## EXAMPLE 8

## Prostaglandins

A. Carboprost thromethamine lingual spray

	Amounts	preferred amount	most preferred amount
5 Carboprost thromethamine	0.05-5	0.1-3	0.25-2.5
water	50-95	60-80	65-75
ethanol	5-20	7.5-15	9.5-12.5
polyethylene glycol	5-20	7.5-15	9.5-12.5
sodium chloride	1-20	3-15	4-8
10 flavors	0.1-5	1-4	2-3

pH is adjusted with sodium hydroxide and/or hydrochloric acid

B. Carboprost non-polar lingual spray

	Amounts	preferred amount	most preferred amount
Carboprost	0.05-5	0.1-3	0.25-2.5
miglyol	25-50	30-45	35-40
Butane	5-60	10-50	20-35
polyoxyethyl-ated	25-50	30-45	35-40
oleic glycerides			
flavors	0.1-10	1-8	5-7.5

15

## EXAMPLE 9

## Neutraceuticals

A. Carnitine as bite capsule (contents are a paste)

	Amounts	preferred amount	most preferred amount
20 Carnitine fumarate	6-80	30-70	45-65
soya oil	7.5-50	10-40	12.5-35
soya lecithin	0.001-1.0	0.005-0.5	.01-0.1
Soya fats	7.5-50	10-40	12.5-35
flavors	6-80	30-70	45-65
soya oil	7.5-50	10-40	12.5-35
25 soya lecithin	0.001-1.0	0.005-0.5	.01-0.1
Soya fats	7.5-50	10-40	12.5-35
flavors	1-10	2-8	3-6

**B. Valerian as lingual spray**

	Amounts	preferred amount	most preferred amount
Valerian extract	0.1-10 0.2-7	0.1-10	0.2-7
5 water	50-95	60-80	65-75
ethanol	5-20	7.5-15	9.5-12.5
polyethylene glycol	5-20	7.5-15	9.5-12.5
flavors	1-10	2-8	3-6

**10 B. Echinacea as bite capsule**

	Amounts	preferred amount	most preferred amount
Echinacea extract	30-85	40-75	45-55
soya oil	7.5-50 10-40		12.5-35
soya lecithin	0.001-1.0	0.005-0.5	.01-0.1
15 Soya fats	7.5-50	10-40	12.5-35
flavors	1-10	2-8	3-6

**B. Mixtures of ingredients**

	Amounts	preferred amount	most preferred amount
20 Magnesium oxide	15-40	20-35	25-30
Chromium picolinate	0.01-1.00.02-0.5	.025-0.075	
folic acid	.025-3.00.05-2.0	0.25-0.5	
vitamin B-12	0.01-1.00.02-0.5	.025-0.075	
vitamin E	15-40	20-35	25-30
25 Soya oil	10-30 15-20	12.5-25 10-40	12.5-35
soya lecithin	0.1-5	0.2-4	0.5-1.5
soya fat	10-30 17.5-20	15-25 10-40	15-35

## EXAMPLE 10

**Sleep Inducers (also CNS active amine)****A. Diphenhydramine hydrochloride lingual spray**

	Amounts	preferred amount	most preferred amount
Diphenhydramine HCl	3-50	4-40	5-35
<u>Diphenhydramine HCl</u>	<u>3-50</u>	<u>4-40</u>	<u>5-35</u>
water	5-90	10-80	50-75
ethanol	1-80	3-50	5-10
polyethylene glycol	1-80	3-50	5-15
Sorbitol	0.1-5	0.2-4	0.4-1.0
aspartame	0.01-0.5	0.02-0.4	0.04-0.1
flavors	0.1-5	1-4	2-3

5

## EXAMPLE 11

**Anti-Asthmatics-Bronchodilators****A. Isoproterenol Hydrochloride as polar lingual spray**

	Amounts	preferred amount	most preferred amount
Isoproterenol Hydrochloride	0.1-10	0.2-7.5	0.5-6
water	5-90	10-80	50-75
ethanol	1-80	3-50	5-10
polyethylene glycol	1-80	3-50	5-15
Sorbitol	0.1-5	0.2-4	0.4-1.0
aspartame	0.01-0.5	0.02-0.4	0.04-0.1
flavors	0.1-5	1-4	2-3

**B. Terbutaline sulfate as polar lingual spray**

	Amounts	preferred amount	most preferred amount
Terbutaline sulfate	0.1-10	0.2-7.5	0.5-6
water	5-90	10-80	50-75
ethanol	1-10	2-8	2.5-5
Sorbitol	0.1-5	0.2-4	0.4-1.0
aspartame	0.01-0.5	0.02-0.4	0.04-0.1
flavors	0.1-5	1-4	2-3

**C. Terbutaline as non-polar lingual spray**

	Amounts	preferred amount	most preferred amount
Terbutaline	0.1-10	0.2-7.5	0.5-6
migylol	25-50	30-45	35-40
isobutane	5-60	10-50	20-35
polyoxyethylated oleic glycerides	25-50	30-45	35-40
flavors	0.1-10	1-8	5-7.5

5

**D. Theophylline polar bite capsule**

	Amounts	preferred amount	most preferred amount
Theophylline	5-50	10-40	15-30
polyethylene glycol	20-60	25-50	30-40
glycerin	25-50	35-45	30-40
propylene glycol	25-50	35-45	30-40
flavors	0.1-5	1-4	2-3

**E. Albuterol sulfate as polar lingual spray**

	Amounts	preferred amount	most preferred amount
Albuterol sulfate	0.1-10	0.2-7.5	0.5-6
water	5-90	10-80	50-75
ethanol	1-10	2-8	2.5-5
Sorbitol	0.1-5	0.2-4	0.4-1.0
aspartame	0.01-0.5	0.02-0.4	0.04-0.1
flavors	0.1-5	1-4	2-3

**Example 12****Polar solvent formulations using a propellant:**

5

**A. Sulfonylurea**

	<u>Amount</u>	<u>Preferred Amount</u>	<u>Most-Preferred Amount</u>
<u>Glyburide</u>	<u>0.1-25%</u>	<u>0.5-15%</u>	<u>0.6-10%</u>
<u>Ethanol</u>	<u>40-99%</u>	<u>60-97%</u>	<u>70-97%</u>
<u>Water</u>	<u>0.01-5%</u>	<u>0.1-4%</u>	<u>0.2-2%</u>
<u>Flavors</u>	<u>0.05-10%</u>	<u>0.1-5%</u>	<u>0.1-2.5%</u>
<u>Propellant</u>	<u>2-10%</u>	<u>3-5%</u>	<u>3-4%</u>

10

**B. Prostaglandin E<sub>1</sub> (vasodilator)**

	<u>Amount</u>	<u>Preferred Amount</u>	<u>Most-Preferred Amount</u>
<u>Prostaglandin E<sub>1</sub></u>	<u>0.01-10%</u>	<u>0.1-5%</u>	<u>0.2-3%</u>
<u>Ethanol</u>	<u>10-90%</u>	<u>20-75%</u>	<u>25-50%</u>
<u>Propylene glycol</u>	<u>1-90%</u>	<u>5-80%</u>	<u>10-75%</u>
<u>Water</u>	<u>0.01-5%</u>	<u>0.1-4%</u>	<u>0.2-2%</u>
<u>Flavors</u>	<u>0.05-10%</u>	<u>0.1-5%</u>	<u>0.1-2.5%</u>
<u>Propellant</u>	<u>2-10%</u>	<u>3-5%</u>	<u>3-4%</u>

**C. Promethazine** (antiemetic, sleep inducer, and CNS active amine)

	<u>Amount</u>	<u>Preferred Amount</u>	<u>Most-Preferred Amount</u>
Promethazine	1-25%	3-15%	5-12%
Ethanol	10-90%	20-75%	25-50%
Propylene glycol	1-90%	5-80%	10-75%
Water	0.01-5%	0.1-4%	0.2-2%
Flavors	0.05-10%	0.1-5%	0.1-2.5%
Propellant	2-10%	3-5%	3-4%

5

**D. Meclizine**

	<u>Amount</u>	<u>Preferred Amount</u>	<u>Most-Preferred Amount</u>
Meclizine	1-25%	3-15%	5-12%
Ethanol	1-15%	2-10%	3-6
Propylene glycol	20-98%	5-90%	10-85%
Water	0.01-5%	0.1-4%	0.2-2%
Flavors	0.05-10%	0.1-5%	0.1-2.5%
Propellant	2-10%	3-5%	3-4%

## WHAT IS CLAIMED IS:

1. A buccal aerosol spray composition for transmucosal administration of a pharmacologically active compound

5 \_\_\_\_\_ provided that where the said active compound is soluble in a pharmacologically acceptable polar solvent said composition comprises in weight % of total composition: aqueous polar solvent ~~75-99.8%~~, 30-99.69%, active compound ~~0.0025-20%~~, 0.001-60%,

~~and where said active compound is soluble in a pharmacologically acceptable non-polar solvent said composition comprises in weight % of total composition: pharmaceutically acceptable propellant \_\_\_\_\_ where said composition additionally comprises a propellant said composition comprises in total weight % of total composition: a propellant selected from the group consisting of C<sub>3-8</sub> hydrocarbon of a linear or branched configuration ~~50-95%~~, 2 - 10%, aqueous  
15 polar solvent 10-99%, and active compound 0.1-25%,~~

\_\_\_\_\_ where said active compound is soluble in a pharmacologically acceptable non-polar solvent said composition comprises in weight % of total composition: non-polar solvent 30-99.69%, active compound 0.005-55%, and

\_\_\_\_\_ where said composition additionally comprises a pharmaceutically acceptable propellant said composition comprises in weight % of total composition: a propellant selected from the group consisting of C<sub>3-8</sub> hydrocarbon of a linear or branched configuration 5-80%, non-polar solvent 20-85%, active ~~non-polar solvent 5-50%~~, active compound ~~0.0025-40%~~, 0.05-50%,

25 \_\_\_\_\_ wherein the active compound is selected from the group consisting of bio-logically active peptides, central nervous system active amines, sulfonyl ureas, antibiotics, antifungals, antivirals, sleep inducers, antiasthmatics, antiemetics, histamine H-2 receptor antagonists, barbiturates, ~~prostoglandins~~ and ~~neutraceuticals~~.

30 prostoglandins, bronchial dilators selected from the group consisting of terbutaline, and theophylline.



2. The composition of claim 1 additionally comprising, by weight of total composition: ~~flavoring agent 0.05-5%~~ agent 0.1-10%.

3. The composition of claim 1 comprising: ~~polar solvent 75-99%, 37-98.58%,~~ active compound ~~0.025-20%, 0.0005-55%,~~ flavoring agent 0.1-2.5%, 0.5-8%.

4. ~~The composition of claim 1 comprising: polar solvent 75-98%, 60.9-97.06%,~~ active compound ~~0.125-12.5%, 0.01-40%,~~ flavoring agent 0.1-2.5%, 0.75-7.5%.

5. The composition of Claim 1 wherein the polar solvent is selected from the group consisting of low molecular weight polyethylene glycols (PEG) of 400-1000 MW, C<sub>2</sub>-C<sub>8</sub> mono- and poly-alcohols, and alcohols of C<sub>7</sub>-C<sub>18</sub> hydrocarbons of a linear or branched configuration.

6. The composition of Claim 1 wherein the solvent is aqueous polyethylene glycol.

7. The composition of Claim 1 wherein the solvent iscomprises aqueous ethanol.

8. The composition of Claim 1 wherein the active compound is selected from the group consisting of cyclosporin, clozapine, glyburide, zidevudine, erythromycin, ~~morphine,~~ odansitron, odansetron, cimetidine, phenytoin, carboprost ~~thromethamine and valerian~~ thromethamine, and valerian in their nonionized form or as the pharmaceutically acceptable salts thereof.

9. The composition of Claim 2 wherein the flavoring agents are selected from the group consisting of synthetic or natural oil of peppermint, oil

of spearmint, citrus oil, fruit flavors, sweeteners and combinations thereof.

10. The composition of Claim 2 of the formulation: polar solvent  
~~75-99%~~, 75-85%, cyclosporin ~~0.12-10%~~, 15-25%, flavoring agent  
5 ~~0.05-5%~~, 0.1-5%.

11. The composition of Claim 2 of the formulation: polar solvent  
~~75-99%~~, 19-90%, odansitron ~~0.0125-10%~~, hydrochloride 2.5-15%, flavoring  
agent ~~0.05-5%~~, 1-10%.

12. A method of administering a pharmacologically active compound to a mammal in need of same, by spraying the oral mucosa of said mammal with a composition of claim 1.

5 13. The method of claim 12 wherein the amount of spray administered is predetermined.

10 14. The composition of claim 1 comprising: propellant ~~55-85%, 5-80%~~, non-polar solvent ~~15-45%, 25-85%~~, active compound ~~0.025-20%, 0.1-40%~~, flavoring agent ~~0.1-2.5%, 1-8%~~.

15 15. The composition of claim 1 comprising: propellant ~~60-80%, 20-70%~~, non-polar solvent ~~19-32%, 30-74.75%~~, active compound ~~0.125-12.5%, 0.25-35%~~, flavoring agent ~~1-2%, 2-7.5%~~.

20 16. The composition of Claim 1 wherein the propellant is propane, N-butane, iso-butane, N-pentane, iso-pentane, or neo-pentane, and mixtures thereof.

25 17. The composition of Claim 1 wherein the propellant is ~~N-butanen~~-butane or iso-butane and has a water content of no more than 0.2% and oxidizing agents, reducing agents, and Lewis acids or bases content in a concentration of less than 0.1%.

30 18. The composition of Claim 1 wherein the solvent is a selected from the group consisting of (C<sub>2</sub>-C<sub>24</sub>) fatty acid (C<sub>2</sub>-C<sub>6</sub>) esters, C<sub>7</sub>-C<sub>18</sub> hydrocarbons of a linear or branched configuration, and C<sub>2</sub>-C<sub>6</sub> alkanoyl esters, and triglycerides of the ~~alcohols thereof~~ corresponding acids.

19. The composition of Claim 1 wherein the solvent is miglyol.

20. The composition of Claim 1 of the formulation: propellant ~~50-95%,~~15-80%, non-polar solvent 5-50%, ~~glyburide 0.12-10%,~~20-85%, ~~clozapine 0.5-30%,~~ flavoring agent 0.05-3%-1-5%.

21. The composition of Claim 1 of the formulation: propellant ~~50-95%,~~15-80%, non-polar solvent 5-50%, ~~erythromycin 0.125-2.5%,~~20-85%, ~~zidovudine 25-35%,~~ flavoring agent 0.05-3%-0.1-5%.

22. The composition of Claim 1 of the formulation: propellant ~~50-95%,~~5-60%, non-polar solvent 5-50%, ~~morphine sulfate~~ 0.125-25%,15-98.5%, ~~carboprost 0.05-5%,~~ flavoring agent 0.05-3%-0.1-10%.

23. The composition of Claim 1 of the formulation: propellant ~~50-75%,~~ non-polar solvent 25-50%, ~~cimetidine hydrochloride 0.0025-2.5%,~~ ~~flavoring agent 0.05-3%-5-60%,~~ non-polar solvent 50-94.8%, ~~terbutaline~~ 0.5-6%, ~~flavoring agent 0.01-10%.~~

~~24. A soft bite gelatin capsule for transmucosal administration of a pharmacologically active compound, where said active compound is at least partially soluble in a pharmacologically acceptable polar solvent, having charged thereto a fill composition comprising in weight % of total fill composition: polar solvent 50-99.8%, emulsifier 0-20%, active compound 0.0003-26%,~~

~~and where said active compound is at least partially soluble in a pharmacologically acceptable non-polar solvent, having charged thereto a fill composition comprising in weight % of total fill composition: non-polar solvent 30-99.8%, emulsifier 0-20%, active compound 0.0003-32%,~~

~~wherein the active compound is selected from the group consisting of biologically active peptides, central nervous system active amines, sulfonyl ureas, antibiotics, antifungals, antivirals, antiemetics, histamine H-2 receptor antagonists, barbiturates, prostoglandins and neutraceuticals, provided that said composition contains less than 10% of water.~~

~~25. The composition of Claim 24 wherein the active compound is selected from the group consisting of cyclosporin, clozapine, glyburide, erythromycin, morphine, odansitron, cimetidine, phenytoin, carboprost~~  
5 ~~thromethamine and valerian~~  
~~in their nonionized form or as the pharmaceutically acceptable salts thereof.~~

10 ~~26. The capsule of Claim 24 wherein the active compound is in their nonionized form or as the free base of the pharmaceutically acceptable salts thereof.~~

~~27. The capsule of Claim 24 wherein the flavoring agents are~~  
15 ~~synthetic or natural oil of peppermint, oil of spearmint, citrus oil, fruit flavors, or sweeteners and combinations thereof.~~

~~28. The capsule of claim 24 additionally comprising, by weight of the fill composition: flavoring agent 0.05-60%.~~

20 ~~29. The soft bite gelatin capsule of Claim 24 comprising as the fill composition: polar solvent 50-99.8%, emulsifier 0-15%, active compound 0.0003-26%, flavoring agent 0.1-50%.~~

25 ~~30. The soft bite gelatin capsule of Claim 24 comprising as the fill composition: polar solvent 70-99.5%, emulsifier 0-10%, active compound 0.015-24.0%, flavoring agent 0.1-50%.~~

~~31. The capsule of Claim 24 wherein the solvent is selected from the~~  
30 ~~group consisting of low molecular weight polyethyleneglycols (PEG) of 400-1000 MW, C<sub>2</sub>-C<sub>8</sub> mono and poly-alcohols, and alcohols of C<sub>7</sub>-C<sub>18</sub> hydrocarbons of a linear or branched configuration.~~

~~32. The capsule of Claim 24 wherein the solvent is selected from low molecular weight polyethyleneglycols (PEG) of 400-600 MW.~~

5 ~~33. The capsule of Claim 24 comprising: non polar solvent 40-99.8%, emulsifier 0-15%, active compound 0.004-26%, flavoring agent 0.1-5%.~~

10 ~~34. The capsule of Claim 24 comprising: non polar solvent 40-99.8%, emulsifier 0-15%, active compound 0.004-26%, flavoring agent 0.1-5%.~~

15 ~~35. The capsule of Claim 24 wherein the solvent is selected from the group consisting of (C<sub>2</sub>-C<sub>24</sub>) fatty acid (C<sub>2</sub>-C<sub>6</sub>) esters, C<sub>7</sub>-C<sub>18</sub> hydrocarbons of a linear or branched configuration, and C<sub>2</sub>-C<sub>6</sub> alkanoyl esters, and triglycerides of the alcohols thereof.~~

20 ~~36. The capsule of Claim 24 comprising as the fill composition the formulation: polar solvent 75-99%, emulsifier 0-20%, morphine 0.01-4%, flavoring agent 0.05-5%.~~

25 ~~37. The capsule of Claim 24 comprising as the fill composition the formulation: polar solvent 55-99%, emulsifier 0-20%, odansitron 0.01-4%, flavoring agent 0.05-5%.~~

~~38. The capsule of Claim 24 comprising as the fill composition the formulation: polar solvent 65-99%, emulsifier 0-20%, cimetidine 0.0003-2%, flavoring agent 0.05-5%.~~

30 ~~39. The capsule of Claim 24 comprising as the fill composition the formulation: polar solvent 75-99.8%, emulsifier 0-20%, phenytoin 0.0003-4%, flavoring agent 0.05-5%.~~

~~40. The capsule of Claim 24 comprising as the fill composition the formulation: polar solvent 75-99.8%, emulsifier 0-20%, 0.02-9.5%, flavoring agent 0.05-5%.~~

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~~41. The capsule of Claim 24 comprising as the fill composition the formulation: polar solvent 75-99.8%, emulsifier 0-20%, valerian 0.02-9.5%, flavoring agent 0.05-5%.~~

10        ~~42.24. A buccal pump spray composition for transmucosal administration of a pharmacologically active compound where said active compound is soluble in a pharmacologically acceptable non-polar solvent said composition comprises in weight % of total composition: non-polar solvent 60%-30-99.69%, 99.9975%, active compound 0.0025-40%, 0.005-55%, flavoring agent 0.1-10%.~~

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~~\_\_\_\_\_ wherein the active compound is selected from the group consisting of bio-logically active peptides, central nervous system active amines, sulfonyl ureas, antibiotics, antifungals, antivirals, sleep inducers, bronchial dilators, antiasthmatics, antiemetics, histamine H-2 receptor antagonists, barbiturates,~~

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~~prostaglandins and neutraceuticals and prostoglandins.~~

25. A buccal pump spray composition for transmucosal administration of a pharmacologically active compound where said active compound is soluble in a pharmacologically acceptable non-polar solvent said composition comprises in weight % of total composition: non-polar solvent 30-99.69%, active compound 0.005-55%, flavoring agent 0.1-10%,
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wherein the active compound is selected from the group consisting of antihistamines, alkaloids, hormones, benzodiazepines and narcotic analgesics.



### ABSTRACT OF THE DISCLOSURE

A ~~buccal aerosol spray~~Buccal aerosol sprays or capsule using apolar  
5 and non-polar solvent ~~hashave~~ now been developed which provides  
biologically active compounds for rapid absorption through the oral mucosa,  
resulting in fast onset of effect. The buccal aerosol ~~spray~~polar compositions of  
the invention comprises formulation I: propellant ~~50-95%~~, ~~non-polar~~  
solvent ~~5-50%~~, aqueous polar solvent 30-99.89%, active compound  
10 0.001-15%, 0.001-60%, optionally containing flavoring agent 0.05-5%. The  
~~soft bite gelatin capsule~~0.1-10%. Propellant 2-10%. The non polar composition  
of the invention comprises formulation II: non-polar solvent ~~55-99.8%~~,  
emulsifier ~~0-20%~~, 20-85%, active compound 0.001-25%, and 0.005-50%, and  
optionally flavoring agent 0.05-5.0%.  
15 0.1-10% and

c:\wp51\phco\0506.pctpropellant 50-80%.

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Phco8b.spc

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